COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Second draft addendum to the 2013 COT statement on potential risks from vitamin A in the infant diet

Introduction

1. The Committee on Toxicity (COT) has been asked to consider the toxicity of chemicals in the infant diet and the diet of young children aged 1-5 years, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. A scoping paper (TOX/2015/32), highlighting some of the chemicals for possible consideration for the diet of young children aged 1-5 years was discussed by the COT in October 2015. Members concluded that a review on the potential risks from vitamin A in the diet of young children aged 1-5 years should be completed.

2. A discussion paper on vitamin A (TOX/2016/40) was presented to Members in December 2016 and the first draft statement was present in February 2017 where some minor amendments were requested. These have been addressed and the latest version with tracked changes can be found attached as annex A to this paper.

Questions to the committee

3. Members are asked to comment on the draft statement addendum attached as annex A, concentrating in particular on the conclusions in paragraphs 49 – 51.

Secretariat
June 2017

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Addendum to the 2013 COT statement on potential risks from vitamin A in the infant diet

Background

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will influence the Government's dietary recommendations for infants and young children. SACN is examining the nutritional basis of the advice. The Committee on Toxicity in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants, most of which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years, but are being considered in two stages, focussing first on infants aged 0 to 12 months, and now on advice for children aged 1 to 5 years.

2. In 2013 the COT issued a statement on potential risks from vitamin A in the infant diet[1]. This addendum to the 2013 statement provides exposure assessments for children aged 1 to 5 years and updates the information for infants. In 2013 the infant age intervals used for expressing exposure were according to the published report of the Diet and Nutrition Survey of Infants and Young Children (DYNSIYC) (DH 2013) and were as follows 4 to <7, 7 to <10 and 10 to<12 and 12 to <19 months. However, following the availability of individual consumption data from DNSIYC exposures in more recent COT papers, including this discussion paper, have been updated and expressed according to the following infant age ranges: 4 to <6, 6 to <9, 9 to <12 months, 12 to <15 and 15 to <18 months.

3. The EC regulations that led to the 2006 Infant Formula and Follow-on Formula (England) regulations, which set out the vitamin A compositional requirements in infant and follow on formula, were amended in 2016 to come into effect in 2020 (European Commission, 2006 and 2016). The amended regulations set out a minimum vitamin A content of 70 µg RE/100 kcal and a maximum vitamin A content of 114 µg RE/100 kcal. The maximum value equates to 77 µg RE/100 mL by applying a conversion ratio of 67 kcal/100mL (FAO/WHO, 2015).

[1] https://cot.food.gov.uk/sites/default/files/cot/cotstavita.pdf

4. Current UK Government guidance regarding vitamin A recommends that, for infants, liver should be avoided if solid foods are introduced before six months. Infants and children over the age of six months should not be given more than one portion of liver per week. Supplements containing vitamins A, C and D should be given to children aged one to five years (DH 2016).

5. The statutory Healthy Start scheme in the UK provides means-tested nutritional help to pregnant women and families with children under four years old who have a very low income and are in disadvantaged circumstances. It gives vouchers for fruit and vegetables, both cow's and formula milk as well as coupons for Healthy Start vitamin supplements. The amount of vitamin A contained within the daily dose of drops is 233 µg RE. The label includes strong advice to keep to the dose recommended and not to give two supplements at the same time (NHS 2016).

6. The COT previously assessed the risks associated with exposure to vitamin A in the infant diet in 2013 by comparison with the infant-specific tolerable upper intake level (TUL) of 200 µg RE/kg bw/day derived by the COT. This exposure level was based on a LOAEL of 800 µg RE/kg bw/day for an endpoint of bulging fontanelles. Members had decided that the Scientific Committee on Food (SCF) TUL allometrically scaled from findings in adults was not appropriate for an infant population. They were uncertain about using allometry to scale from adults to children, noting that it is usually used to scale between species. They decided that the endpoint of bulging fontanelles, as used by the Institute of Medicine (IOM), would be more appropriate and that a smaller uncertainty factor than the default of ten used by the IOM should be applied.

Vitamin A

7. Vitamin A is a group of fat-soluble vitamins which are available from the diet as either preformed vitamin A or provitamin A. High intake of provitamin A is not associated with the same risks as high intake of preformed vitamin A (COT 2013), therefore in line with the previous statement, this discussion paper focuses on preformed vitamin A.

8. Vitamin A is quantified either in international units (IU) or µg retinol equivalents (RE). The total vitamin A content of the diet is usually expressed as RE. For consistency, RE is used throughout this statement. Corresponding IU values can be approximated by multiplying the RE by 3.33; however, this will only be accurate if the vitamin A is entirely in the form of retinol. RE can be calculated with certainty only if the relative amounts of the different forms of preformed vitamin A and provitamin A carotenoids are known.

Toxicity

9. Initial clinical features of vitamin A toxicity in age groups other than infants are lethargy, pain in the joints, dry skin, headache and nausea and

vomiting, although this varies depending on severity. More severe signs that can diagnose hypervitaminosis A clinically include alopecia, drowsiness, liver and bone damage and visual problems (Loughrill 2016, SCF 2002). Additional information regarding clinical effects of chronic hypervitaminosis A in children was available in a review by Biesalski (1989) cited by the SCF (2002). Biesalski (1989) stated that a long-term dose of 18000-60000 IU (5405-18018 µg RE/day) vitamin A could be expected to cause toxicity in children. Biesalski also reported that the consequences of chronic hypervitaminosis A in children are dominated by changes in the skeletal system, premature epiphyseal closing, thickening of the cortical regions of long bones and subsequently retarded growth.

10. Persistently b~~B~~ulging fontanelles that are reversible following elimination of supplementation (IOM 2001) are a common clinical sign of vitamin A toxicity in infants; however this symptom is not reported in older infants whose fontanelles have fused. A bulging fontanelle is not usually accompanied by an elevation in intracranial pressure as it is assumed that the increased volume of the cerebro-spinal fluid can expand using the fontanelles and un-fused cranial sutures. In older children and adults with hypervitaminosis A, headaches may be a manifestation of elevated intracranial pressure (SCF 2002). Babikian *et al* (1994) reported that the most common symptom in children with idiopathic intracranial hypertension was headache, with 63% of patients reporting this sign. However raised intracranial pressure is not described or stated as being measured in case reports and is not routinely measured, therefore the COT thought that it would not be appropriate to have bulging fontanelles or raised intracranial pressure as an endpoint for children over the age of 12 months.

11. The SCF considered hepatotoxicity to be one of the most severe outcomes of chronic hypervitaminosis A, with the mechanism thought to be related to overload of the storage capability for vitamin A in the liver. Human data is limited to case reports, with the evidence of causal link the slow improvement of symptoms after withdrawal of vitamin A. However in some cases the hepatotoxicity progresses and can be fatal. The proportion of vitamin A induced hepatotoxicity that can be reversed is difficult to estimate with various conditions (e.g.chronic alcohol intake) potentiating the damage caused by overdosing on vitamin A. From the available data, toxicity in humans is linked to both the dose regularly ingested and the duration of the dosing.

12. The SCF reviewed cases of hypervitaminosos A reported by Bauernfeind (1980) which included two cases of acute poisoning resulting in hepatotoxicity. A 31 year old woman took 1060000 RE/ day for three weeks in an emulsion and developed vomiting, thirst, headaches, alopecia, scaly skin, hypercalcaemia, hepatosplenomegaly and hepatitis. Once the medication was stopped she recovered over the period of one month. A 30 year old man ingested 15500000 RE over a period of 22 days. He suffered dizziness, headaches, visual disturbances, scaly skin, renal failure, hepatomegaly, hypercalcaemia and hyperlipidaemia. No further information was available on this case. Bauernfeind (1980) reported after reviewing adult cases that the

toxic effects of vitamin A develop in a shorter time period when very high levels are taken than when moderate levels are taken. When 303000 µg RE or more is taken daily toxic effects may present within weeks or days, if intake is between 120000 -210000 µg RE daily then effects may manifest after one to 36 months. When ingesting 45000-60600 µg RE daily it may take 6-85 months to produce signs of toxicity and 6-108 months if consuming 30300 µg RE per day.

13. The most comprehensive report evaluated by the SCF was a group of 41 cases reported by Geubel *et al* (1991) which included reliable intake data for 29 patients. The patients were diagnosed with vitamin A hepatotoxicity on the basis of specific histology (fat-storing cell [FSC] hyperplasia and hypertrophy with indented nuclei and fluorescent vacuoles under ultraviolet light microscopy), a compatible clinical history and the absence of other detectable causes of chronic liver disease and FSC hyperplasia. Only 31.7% (n=13) of the cases were suspected to have vitamin A caused liver toxicity before biopsy of the liver; systemic vitamin A toxicity was established in 20 cases. Most of the patients were taking vitamin A for a dermatological condition; with 26 of the patients taking vitamin A continuously. Alcohol intake was recorded as low in 36 patients, moderate in 4 and high in 1. A precise appraisal of vitamin A intake was possible in 29 patients who had a mean intake of 28770 µg RE/day (range 6000-120000 µg RE) and duration of dosing of 7.17 years (range 0.2-15 years). The patients who were the most severely affected and had developed cirrhosis, ingested significantly more vitamin A (daily and total dose) than those that did not develop cirrhosis. The lowest continuous daily dose found causing cirrhosis was 7500 µg RE/day for six years; a patient who had taken 30300 µg RE/day for two and a half years had similar histology. Cirrhosis also resulted in a patient who had discontinuously taken 90900 µg RE/day over ten years. During a mean follow-up period of four and a half years, nine patients had died from liver disease and three had disease progession.

14. The SCF (2002) found a similar case where eventual death resulted from a 45 year old woman taking an over the counter supplement containing 7500 µg RE/day for over six years. The SCF found that cases of hepatotoxicity have not been reported below 7500 µg RE/ day, and that it can be hypothesized that this value might be the upper threshold of the storage capabilities of the liver. It is not known if a dose lower than 7500 µg RE/day could induce hepatotoxicity if taken for more than 6 years, but such low intakes may not been considered by physicians when they attempted to identify the cause of their patient's liver disease. When considering vitamin A induced hepatotoxicity, the SCF (2002) considered that on a weight basis children were not more sensitive than adults.

15. The SCF (2002) established a TUL for adults of 3000 µg RE/day based on teratogenicity data, and considered this to be applicable to all adults as it was only 2.5-fold less than the lowest chronic daily intake associated with hepatotoxicity

16. The SCF (2002) extrapolated TULs for children from the TUL for adults (3000 µg RE/day) with correction for differences in basal metabolic rate using scaling according to body surface area (bodyweight$^{0.75}$), the exact method of

scaling was not given in the opinion. The TUL was 800 µg RE/day for children aged 1-3 years and 1100 µg RE/day for children aged 4-6 years.

17. In 2015 the EFSA panel on dietetic products, nutrition and allergies reviewed the dietary reference values for vitamin A. They considered that in adults a liver retinol concentration of 20 µg retinol/g liver maintains plasma retinol concentrations, to provide adequate stores and prevent deficiency. They considered that due to a lack of specific data the same value could be used for infants and children. The value for children is calculated using values specific to children for body weight and liver/body weight ratio and an age specific growth factor. They concluded that average requirements for infants and children up to the age of six years were 190µg RE/day for 7-11 months, 205 µg RE/day for 1-3 years and 245 µg RE/day for 4-6 years. The population reference intakes were 250 µg RE/day for 7-11 months and 1-3 years and 300 µg RE/day for 4-6 year.

18. Due to a lack of data specific to children in the SCF review a literature search was performed. The case reports thought to be most relevant are described below.

Case reports of vitamin A toxicity in children

19. A 4 year old boy presented to the emergency department with a history of lethargy, vomiting, headaches that mainly occurred at night, sores, pain in the legs and feet and a pruritic rash covering the legs and trunk. On examination an enlarged lymph node and a small meatal ulcer was found. Blood tests revealed raised erythrocyte sedimentation rate, C-reactive protein level, aspartate aminotransferase and albumin. An infection was found and the child was treated with oral antibiotics and intravenous fluids, however his condition did not improve. Six days later he was transferred to a different hospital, his condition now included oedema, hepatomegaly and hyperkeratosis and hyperpigmentation. It transpired that the boy had been taking 30000 IU (500 µg/kg bw) of retinol daily for 11 months, then 25000 IU (417 µg RE/kg bw) daily the month preceding his admission to hospital. These had been prescribed by a chiropractor to ‘build up his strength’ as they had identified that he had food allergies. Chronic hypervitaminosis A was diagnosed and the vitamin A was stopped, blood tests showed hypercalcaemia. Three days after admission he was discharged with just some residual tenderness of the soles of his feet. Five weeks later his serum retinol level was still elevated at 2.17 µmol/L (normal range 0.5-1.5 µmol/L) (Patel et al, 1988).

20. Mendoza et al (1988) reported the case of a three year old girl who was failing to thrive. She had a history of two months of pain in her lower

extremities, lethargy, erythematous skin that was peeling, a protuberant abdomen and periods of refusing to walk. On examination she was thin, had dry skin and had a head circumference that was at the tenth percentile. All bloods tested were normal. After two weeks she was admitted with ascites and respiratory distress, her abdomen was greatly distended and she had alopecia. Investigations revealed mildly elevated liver enzymes and right pleural effusion. A liver biopsy showed evidence of some sclerosis. On further questioning it was discovered that the child had been given 2730 RE µg/kg bw/day vitamin A for one week and then 1365 µg RE/kg bw/day for six months finishing one month before her presentation. An initial vitamin A serum level was normal, only when it was repeated after eight weeks was it found to be elevated 838 IU/dL.

21. A boy, 2 years and 9 months old, developed pruritis, xerosis of the skin, sensitivity to light, loss of ambulation and bone pain. X-rays showed thickening of the mid-shaft of one fibula and a bone scan increased uptake of tracer within the femur and fibula. Bloods were normal except for an elevated alkaline phosphatase at 396 IU/L (normal range 70-160 IU/L). On repeated questioning the mother reported that she had been giving the child multivitamins prescribed by a nutritionist. He had been receiving 1903 µg RE/kg bw/day vitamin A for a period of five months for a diarrhoeal disease that did not resolve. The vitamins were stopped and within one week his walking and rash improved, the light sensitivity and lethargy remained for two months. Two weeks after the diagnosis was made the boy's hair started to fall out, it took four months before it started to return (Gamble and Stanley, 1985).

22. A boy, three years old, started to complain of severe pain in his legs. In his first six months his growth was poor and he had persistent otitis media. Radiographs showed that he had new formation of bone on both tibias, femurs and his right radius. He also had hypercalcaemia, a raised intracranial pressure and splayed cranial sutures. The following year otitis returned and his intracranial pressure was still high warranting a ventriculoperitoneal shunt. He then developed alopecia, an exfoliative rash, liver disease and ascites. He died from renal failure associated with pneumonia, coagulopathy and sepsis. Multivitamins containing 2500 IU (750 µg RE) vitamin A had been used intermittently during his first nine months of life and 450 IU (137 µg RE) vitamin A was given in a ten day multivitamin course in his second year. He did however eat chicken liver spread sandwiches (approximately 25g chicken liver fried in fat) two to three times a week. The boy's younger brother who had the same diet reported otitis media, leg pain, nausea and vomiting and papilledema at the age of two and a half years. His long bones were normal but he had splayed cranial sutures. He was found to be hypercalcaemic. During his third year he developed alopecia, an exfoliative rash, bone pain, hepatomegaly, splenomegaly, pleural effusion and ascites. His serum retinol was found to be 101 µg/dL (normal 30-60 µg/dL) and his retinyl esters 485 µg/dL (normal <7 µg/dL). Samples of three of the brands of chicken liver were tested for vitamin A content and an estimate of the vitamin A content of the chicken liver spread sandwiches was made, the daily intake including other

sources was thought to total 15000 IU (4550 µg RE, 283 µg RE/kg bw/day, assuming a bodyweight of 16.1kg [Bates 2014]) (Carpenter et al, 1987).

23. Miller and Hayon (1985) reported the case of a three year old with mosaic Down syndrome who was admitted to hospital for pneumonia. He had developed muscle spasm, discomfort on standing and abdominal pain in the preceding week. The child had desquamation of the skin and alopecia, blood tests revealed elevated liver enzymes. A bone scan showed an increased uptake of tracer in the diaphyseal regions of his femurs, tibias, fibulas and ulnas and in his cranial sutures. Radiographs showed new bone along the tibia and fibulas. He had been receiving 20000 IU /day (6060 µg RE, 376 µg RE/kg bw/day, assuming a bodyweight of 16.1kg [Bates 2014]) of vitamin A for one year, subsequent serum vitamin A levels were elevated 867 IU/dL (normal 65-275). The vitamins were stopped and his liver enzymes returned to normal and a repeat bone scan four and a half months later showed no increased uptake of tracer.

24. Lippe et al (1981) reported two cases of hypervitaminosis A. The first was a four year old boy who was reported to be in good health until six months prior to admission. He presented with increased intracranial pressure, bone pain and oedema of the face and extremities after having increased frequency of upper respiratory illness. The child had been taking supplements containing 15000 IU/day (4505 µg RE, 246 µg RE/kg bw/day, assuming a bodyweight of 18.3kg Bates 2014) vitamin A for three months, during which he had developed pruritic erythematous papular eruptions on his skin. After three months the vitamin A was increased to 250000 IU/day (75075 µg RE, 4102 µg RE/kg bw/day, assuming a bodyweight of 18.3kg [Bates 2014]) as the respiratory illness had not abated. Within two weeks of starting the new regimen he developed nausea and vomiting, bone pain, peeling and blistering of the mucosa of the lips, restlessness and hyperactivity. All supplementation was stopped and the symptoms improved. However four days before admission he had become unwell again and examination revealed hepatomegaly, bone tenderness and oedema of extremities. Bloods showed hypercalcaemia, a raised alkaline phosphatase and a serum vitamin A of 1626 IU/dL. Radiographs showed metaphyseal bands of increased calcium without formation of new bone. Scans of his brain showed findings consistent with pseudotumor cerebri.

25. The second case from Lippe et al (1981) was the presentation of a two and a half year old boy previously diagnosed with Pierre Robin syndrome with a pruritic rash over his face and trunk, oedema of face and extremities, fever and bone pain. The child was in the tenth percentile for his height and weight and ophthalmologic examination revealed blurred discs. The patient‘s bone pain meant that he refused to walk. He had hypercalcaemia, an elevated alkaline phosphatase and a serum vitamin A of 1812IU/dL. The child had been taking 25000IU (7508 µg RE, 536 µg RE/kg bw/day, assuming a bodyweight of 14kg [Bates 2014]) vitamin A every day or alternate day plus one or two multivitamins containing 5000 IU of vitamin A and vitamin drops

that also contained vitamin A. Once the patient had developed a rash the mother also applied a cream containing vitamin A (unknown strength).

26. A 4 year old boy presented with poor appetite, an intermittent fever, severe abdominal pain, cracking lips and agonising pain in both legs. After a further 2 weeks being treated at the local district hospital and a partial improvement in symptoms, the skin on his hands and feet started to peel and he developed a papular rash on his back. On admission his scalp hair was scarce and weak, the skin on his face and shins was shiny and his tibiae were thickened and painful. Bloods revealed a mild anaemia, and elevated aspartate aminotransferase and alkaline phosphatase. On day three of admission he developed a bony swelling in the mid-thigh and forearm. Radiography revealed thickening of the periosteum along widened diaphyses of all long bones with lifting of the periosteum in the mid-shaft of ulnar bones and right femur, scintigraphy displayed areas suggestive of multifocal osteoblastic skeletal lesions. The effects seemed to be largely consistent with vitamin A toxicity and on further questioning the parents informed them that they had been giving him 600000 IU (180180 µg RE, 9846 µg RE/kg bw/day, assuming a bodyweight of 18.3kg [Bates 2014]) vitamin A every day for over three months. A serum retinol level was raised at 4.19 µmol/L (normal range 1.13-2.63 µmol/L). After stopping the supplements, the AST normalised and the boy was able to walk within 2 weeks. After two months his bone lesions resolved (Baineni 2016).

27. A girl 15 months old was admitted to hospital after failure to thrive and an increasing head size over the previous 8 months. The child had shiny skin, severe alopecia, and bone tenderness but no musculoskeletal deformities. Radiographs showed a fracture of the right humerus and new bone formation on the left arm and leg. Both distal femoral shafts had abnormal tabulation and the proximal tibial epiphyses were impressed into the cup-shaped metaphyses. Over the previous 7 months the mother had administered 50,000 IU daily (15150 µg RE, 1430 RE/kg bw/day, assuming a bodyweight of 10.6 kg). Serum vitamin A was 195 mcg/100mL (normal 40 mcg/100mL). Vitamin A was stopped and bilateral subdural hematomas were diagnosed and treated. Two months later the patient had improved and had no further symptoms. However at age 2 years 3 months she developed hip and knee flexion contractures, at 3 years 5 months the metaphyses of both femora and tibiae were widened. At 4 years there were fixed flexion contractures of both knees and hips. She was then lost to follow-up until she developed thoracic scoliosis. The authors could not conclude whether the scoliosis was an independent lesion or related to the hypervitaminosis A (Ruby and Mital 1974).

28. All of the doses of vitamin A reported in the above case studies are higher than the TULs derived for children by the SCF. The lowest dose reported in the studies is around five-fold that of the relevant SCF TUL and the highest dose nearly 200-fold, indicating that there is no evidence that the TULs derived by the SCF would not be protective against adverse effects.

Vitamin A exposures in infants and young children aged 0 months to 5 years

New data on sources of vitamin A exposure

29. There were no new data for vitamin A levels in breast milk from the UK. Occurrence data used for estimating exposure from human milk in the 2013 COT statement were used to estimate exposure from this route in this paper.

30. There were no new UK data for vitamin A levels in infant formula. Therefore values used for exposure assessment were taken from the 2013 COT statement. The upper end value of this range (82 µg RE/100 mL) marginally exceeds the maximum value set by the amended EC regulations (77 µg RE/100 mL). The upper end value of the range of levels of vitamin A for different infant formulas as well as the maximum value from the amended EC regulation will be used in the exposure assessment from this source.

31. The concentration of vitamin A in other foods included in the exposure assessments of this paper were derived from food composition databases (McCance and Widdowson, 2015) that support the National Diet and Nutrition Survey (NDNS) (Bates et al., 2014) and the DNSIYC (DH, 2013).

32. There were no new UK data for vitamin A levels in supplements that are marketed for infants and young children. Therefore the values used in the exposure assessments in this paper were as in the 2013 COT statement; the highest dose would provide 757 µg RE/day vitamin A at the recommended dose for ages 0 to 12 months and 1500 µg RE/day for a child aged 12 months and above.

Exposure Assessment

Infants exclusively fed on breast milk or infant formula

33. Exposures for exclusively breastfed or exclusively infant formula fed infants have been calculated assuming values of 800 mL and 1200 mL, for average and high-level daily consumption respectively. Bodyweight data for infants aged 4 to <6 months are from DNSIYC (DH, 2013), with an average of 7.8 kg. Since DNSIYC did not include infants younger than 4 months, a value of 5.9 kg for infants aged 0-3 months, from an older survey (DH, 1994), is applied to infants aged 0-<4 months.

34. Mean and high-level intake of vitamin A in exclusively breastfed infants, based on the upper end of the reported range of vitamin A concentrations in breast milk of 70 µg RE/100 mL are in the region of 72 to 95 µg RE/kg bw/day and 110 to 140 µg RE/kg bw/day, respectively (Table 1). Vitamin A supplement intake by lactating mothers in the UK would be

expected to potentially increase levels of vitamin A in breast milk by less than two-fold. Thus, the estimated vitamin A intake of an infant breastfed by a mother taking vitamin A dietary supplements would be less than twice the highest value of 140 µg RE/kg bw/day in Table 1 i.e. less than 280 µg RE/kg bw/day.

35. Table 1 also shows the estimated vitamin A exposure of exclusively formula fed infants, based on a vitamin A concentration at the new EU maximum regulatory limit for infant formula 77 µg RE/100 mL. Using this limit, mean and high level exposure for 0 to 6 month old infants were up 100 and 160 µg/kg bw/day, respectively. These exposures are similar to those that are derived from the upper end of the range (82 µg RE/100 mL) for major brands of infant formula.

Table 1 Vitamin A exposure (µg RE/kg bw/day) from exclusive feeding on breast milk or infant formula.

	Age in months (consumption volume)[a]			
	0-<4 (800 mL)	**0-<4 (1200 mL)**	**4-<6 (800 mL)**	**4-<6 (1200 mL)**
Breast milk (70 µg RE/100 mL)	95	140	72	110
Formula milk[b] (77 µg RE/100 mL)	100	160	79	120
Formula milk (82 µg RE/100 mL)[c]	110	170	84	130

[a] *Exposures were calculated using an average bodyweight of 5.9 kg for 0 to <4 month olds and 7.8 kg for 4 to <6 month olds*.
[b] *Based on the recent EU regulatory limit of* 77 µg RE/100 mL
[c] *Based on the upper-end of the range for major brands of UK infant formula, as reported previously(COT 2013) .*
Data reported to 2 significant figures.

Infants and young children also consuming other foods

36. Consumption data (on a bodyweight basis) from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), and from the NDNS (Bates et al., 2014) have been used for the estimation of dietary exposures for ages 4 to 18 months, and 18 to 60 months, respectively. The combined daily exposure to vitamin A from breast milk, infant formula and other foods in infants and young children is reported in Table 2. The total (excluding supplements) mean and 97.5th percentile dietary exposure to preformed vitamin A at ages 4 to 60 months ranged from 38 to 79 µg RE/kg bw/day and 93 to 210 µg RE/kg bw/day, respectively.

Table 2 Total dietary exposure to preformed vitamin A from breast milk, infant formula and other food sources, excluding supplements

Total daily exposure of preformed vitamin A (µg RE/kg bw/day)	Age group (months)						
	4-<6	6-<9	9-<12	12 - <15	15 - <18	18 - <24	24 - <60
Mean	62	79	74	59	53	45	38
97.5th percentile	210	200	190	130	120	93	95

Data reported to 2 significant figures

37. The contribution of infant formula to the total average vitamin A daily exposure decreased from 39% at 4 to 6 months to 12% at 12 to 18 months of age (DH, 2013). Likewise, the contribution of breast milk decreased from 15% at 4 to 6 months to 2% at 12 to 18 months of age. Commercially available infant foods provided approximately 24% throughout the first year. Other major contributors to the total exposure were foods not specific to infants such as vegetables and potatoes, and milk and milk products (DH, 2013).

38. For young children aged 18 to 36 months, the major food groups contributing to the total vitamin A daily exposure were: milk and milk products as well as the vegetables and potatoes group (DH, 2013). This was also reported to be the case for children up to the age of 10 years (Bates et al., 2016).

Exposure in consumers of liver

39. DNSIYC and NDNS consumption data were used to estimate exposure to vitamin A from liver, based on all types of liver. Liver pate, which tends to

be eaten in smaller portions than liver itself, was not included in the estimation of exposure (Table 3). The highest intakes averaged over the four days of the survey were evident in the 9 to <12 (160 µg/kg bw/day) and 24 to <60 month (110 µg/kg bw/day) age categories. These data are based on very small numbers of consumers, but indicate that some infants and young children do eat liver and the possible vitamin A intakes from this source.

Table 3 Consumption of liver and exposure to vitamin A in consumers of all types of liver.

	Age group in months (number of consumers)						
	4-<6 (0)	6-<9 (6)	9-<12 (6)	12 - <15 (1)	15 – 18 (2)	18 - <24 (1)	24 - <60 (5)
Mean liver consumption (g/kg bw/day)	n/a	0.41	0.96	0.010	0.24	0.41	0.64

Maximum liver consumption (g/kg bw/day)	n/a	0.52	2.4	0.010	0.41	0.41	2.0
Mean vitamin A exposure (µg/kg bw/day)	n/a	57	160	2.6	25	80	110
Maximum vitamin A exposure (µg/kg bw/day)	n/a	87	410	2.6	43	80	350

Data reported to 2 significant figures

Dietary supplements

40. Potential exposure from vitamin supplements alone at ages 0 to 12 months, based on the brand providing the highest dose of vitamin A in this

age group (757 µg RE/day), was reported previously (COT 2013). Table 4 provides updated estimates for infants, based on the revised age range, as noted in paragraph 2, and also estimates for ages 1-5 years. Use of supplements in the 0 to 6 month age group could lead to total exposures of 220 and 240 µg RE/kg bw/day, if mean exposure from exclusive consumption of breast milk or infant formula is added, respectively; the corresponding exposure arising from use of supplements in infants and young children in addition to high-level exposure from exclusive consumption of breast milk or infant formula is 270 and 300 µg RE/kg bw/day, respectively. For ages 4 to 12 months, supplementation in addition to mean and high-level exposure from the rest of the diet[2,] leads to total exposure ranging from 150 to 170 µg RE/kg bw/day and 270 to 310 µg RE/kg bw/day, respectively (Table 4).

41. The highest dose of vitamin A in daily doses of multivitamin supplements recommended by manufacturers for children older than 12 months is 1500 µg RE/ day (paragraph 26). For ages 12 to 60 months, use of supplements at this dose in addition to mean and high-level vitamin A exposure from the rest of the diet leads to total exposure ranging from 130 to 200 µg RE/kg bw/day and 190 to 270 µg RE/kg bw/day, respectively (Table 4).

42. Exposure to vitamin A from vitamin drops which are provided under the Healthy Start scheme (paragraph 5) at the dosage of 233 µg/day for infants 6 months and over were reported previously (COT 2013). Use of these drops in infants and young children could lead to total exposures of up to 110 and 230 µg RE/kg bw/day, if exposure from these drops are added to the mean and high-level exposure from the rest of the diet, respectively.

[2] Rest of the diet includes breast milk and infant formula as well as other foods, excluding supplements

Table 4 Exposure to vitamin A from supplements (at a dose of 757 and 1500 µg RE/day for infants 0 to 12 months and young children 12 to 60 months, respectively) alone and with contribution from the rest of the diet at ages 0 to 60 months.

Vitamin A Exposure	**Vitamin A exposure (µg/kg bw/day) by age group (months)**							
	0 – <4	**4 - <6**	**6 - <9**	**9 - <12**	**12 - <15**	**15 - <18**	**18 - <24**	**24 - <60**
Vitamin supplements alone [a]	130	97	87	79	140	130	130	93
Vitamin supplements plus **mean** level exposure from **exclusive consumption of breast milk**[a]	220	170	n/a	n/a	n/a	n/a	n/a	n/a
Vitamin supplements plus **high level** exposure from **exclusive consumption of breast milk**[ab]	270	210	n/a	n/a	n/a	n/a	n/a	n/a
Vitamin supplements plus **mean** level exposure from **exclusive consumption of infant formula**[ab]	240	180	n/a	n/a	n/a	n/a	n/a	n/a
Vitamin supplements plus **high-level** exposure from **exclusive consumption of infant formula**[ab]	300	230	n/a	n/a	n/a	n/a	n/a	n/a
Vitamin supplements plus **mean** level exposure from the rest of the diet[c]	n/a	160	170	150	200	180	180	130
Vitamin supplements plus **high-level** exposure from the rest of the diet[c]	n/a	310	290	270	270	250	220	190

[a] *Calculated using average bodyweights of 5.9, 7.8, 8.7, 9.6, 10.6, 11.2, 12.0 and 16.1 kg for 0-<4, 4-<6, 6-<9, 9-<12, 12-<15, 15-<18, 18-<24 and 24-<60 month olds, respectively.*

[b] *The exposure from breast milk (at a vitamin A concentration of 70 µg RE/100mL) and infant formula (at a vitamin A concentration of 82 µg RE/100mL) are as reported in Table1*

[c] *Exposures from the rest of the diet are as reported in Table 2.*

Data reported to 2 significant figures

Table 5 Exposure to vitamin A from vitamin drops provided under the Healthy Start scheme at a dose of 233 µg/day with contribution from the rest of the diet at ages 6 to 60 months

Vitamin A Exposure	**Vitamin A exposure (µg/kg bw/day) by age group (months)**					
	6 - <9	**9 - <12**	**12 - <15**	**15 - <18**	**18 - <24**	**24 - <60**
Vitamin supplements alone (µg/kg bw/day)[a]	27	24	22	21	19	14
Vitamin supplements plus **mean** level exposure from the rest of the diet[b]	110	98	81	74	64	52
Vitamin supplements plus **high-level** exposure from the rest of the diet[b]	230	210	150	140	110	110

[a] *Calculated using average bodyweights of 8.7, 9.6, 10.6, 11.2, 12.0 and 16.1 Kg for 6-<9, 9-<12, 12-<15, 15-<18, 18-<24 and 24-<60 month olds, respectively*
[b] *Exposures from the rest of the diet are as reported in Table 2*
Data reported to 2 significant figures

Risk characterisation

42. Potential risks from the exposure of infants to vitamin A from the diet were characterised by comparison to the TUL of 200 µg RE/kg bw/day established by the COT. This was based on the endpoint of bulging fontanelles, which is specific to infants.

43. The SCF set TULs for children at 800 µg RE /day for those aged 1-3 years and 1100 µg RE/day for those aged 4-6 years. These values were extrapolated from an endpoint of teratogenicity using allometric scaling. The COT considered the SCF TULs for children over 12 months but decided that they were not appropriate as the endpoint of teratogenicity was not relevant to this age group. However the SCF noted that basing the TUL on teratogenicity would also be protective for hepatotoxicity which was observed at exposures 2,5 times greater than those causing teratogenicity. The COT derived infant TUL is 200 µg RE/kg bw/day, comparing the SCF TULs to this show them to be rather conservative. The COT concluded that the most relevant endpoint for children would be hepatotoxicity, but decided that data in children was too limited to derive a safe upper level for hepatotoxicity. Although the SCF TULs for children were based on teratogenicity as this was a more sensitive end point than hepatotoxicity in adults, based on the case reports in children the COT considered these were likely to be suitably protective for hepatotoxicity for the age groups of 1 - 3 years and 4-6 years.

44. Exposures to vitamin A for infants fed exclusively on breast or formula milk are all below the TUL For infants over 4 months and up to 12 months exposed to vitamin A from breast milk, infant formula and other foods there is a small exceedance of the TUL between 4-6 months, however this is only for a short period of time.

45. Table 6 shows the comparison of vitamin A exposures from the supplement providing the highest dose of vitamin A (757µg) plus exclusive breast milk and infant formula, in relation to the TUL. The contribution to exposure from the rest of the diet in relation to the TUL for infants aged 0-12 months is also shown. For the age group 0 <4 months, all exposures except for the vitamin supplement alone exceed the TUL, exceedances however would only be for a short period. Infants aged 6-12 months who are high-level consumers, all exceed the TUL. However it is important to note that the data are adjusted using average bodyweights for each age group, and it is possible that high-level consumers have higher than average bodyweights.

46. The dietary exposures for vitamin A in children aged 12-60 months for the vitamin supplement providing the highest dose of vitamin A (1500 µg) range from 93-140 µg RE/day. The supplement plus mean exposure from the rest of the diet ranges 130-200 µg RE/day and the supplement plus high-level exposure from the rest of the diet is between 190-270 µg RE/day. The exposures for high-level consumers at ages 12-18

months are higher than the levels reported in the case described by Lippe et al (1981). However no weight was reported for the child presented in the case therefore an average weight was used to calculate the dose of vitamin A per kilogram bodyweight; this could be an underestimation of the dose consumed by the child.

47. The dietary exposures to vitamin A from the supplement provided by the Healthy Start scheme for ages 6-60 months, range from 14-27 µg RE/day. The supplement plus mean exposure from the rest of the diet ranges between 52-110 µg RE/day and for the supplement plus high-level exposure from the rest of the diet 110-230 µg RE/day. The age group 0-<6 months has not been included, as the Healthy Start vitamins are not recommended in infants under 6 months of age.

48. The available data specifically on consumption of liver by infants and children indicate that those consuming large amounts could exceed the TUL and exceed the lower levels of vitamin A exposure described in the case reports. In these data the vitamin A intake, primarily from a single eating occasion is based on a small number of consumers and is averaged over the four reporting days of DNSIYC, and it is uncertain if the TUL would be exceeded if the intake were averaged over a longer period of time. However, this assessment and the 2013 COT statement suggest that the current Government recommendation that infants and children over the age of 6 months should not have more than one portion of liver per week is appropriate.

Table 6 Exposure to vitamin A from supplements alone (dose of 757 µg RE/day) and with contribution from the rest of the diet and comparison to the TUL at ages 0 to 12 months

Source of exposure	0-<4 months		4-<6 months		6-<9 months		9-<12 months	
	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL	Exposure (µg/kg bw/day)	%TUL
Vitamin supplements alone	130	65	97	49	87	44	79	40
Vitamin supplements plus mean level exposure from exclusive consumption of breast milk[ab]	220	110	170	85	N/A	N/A	N/A	N/A
Vitamin supplements plus high level exposure from exclusive consumption of breast milk[ab]	270	140	210	110	N/A	N/A	N/A	N/A
Vitamin supplements plus mean level exposure from exclusive consumption of infant formula[ab]	240	120	180	90	N/A	N/A	N/A	N/A
Vitamin supplements plus high-level exposure from exclusive consumption of infant formula [ab]	300	150	230	120	N/A	N/A	N/A	N/A
Vitamin supplements plus mean level exposure from the rest of the diet[c]	N/A	N/A	160	80	170	85	150	75
Vitamin supplements plus high-level exposure from the rest of the diet[c]	N/A	N/A	310	160	290	150	270	140

[a] *Exposure data from exclusive feeding on breast milk or infant formula (Table 1).*
[b] *Calculated using average bodyweights of 5.9, 7.8, 8.7, 9.6, 10.6, 11.2, 12.0 and 16.1 kg for 0-<4, 4-<6, 6-<9, 9-<12, 12-<15, 15-<18, 18-<24 and 24-<60 month olds, respectively. The exposure from infant formula is based on the upper end of the value from the range 63-82 µg/kg bw/day for major brands of UK infant formula.*
[c] *Rest of the diet includes breast milk and infant formula and other foods, excluding supplements (Table 2).*
Data reported to 2 significant figures

Conclusions

49. The COT concluded that the TUL based on an endpoint of bulging fontanelles was appropriate to evaluate vitamin A exposures in infants. However no TULs could be established for the ages 12-60 months on the basis of the currently available data.

50. High- level consumers are over or approaching levels of vitamin A reported in the literature as causing toxicity and the possibility of adverse effects from these levels cannot be excluded. However if effects did occur they would only be in a small proportion of consumers.

51. Though the data on liver consumption are limited, frequent consumption could be a cause for concern and that the current Government recommendations that infants over six months old should not have more than one portion of liver per week is appropriate.

~~52. Although some of the current intakes are approaching or above the lowest level causing toxicity reported in the literature there appears to be no indication of adverse effects in the population. Therefore, the COT concluded that at current intakes, vitamin A is unlikely to pose a risk to health, but that levels should continue to be monitored.~~

Secretariat
June 2017

References

Babikian, P., Corbett, J., Bell, W. (1994) Idiopathic intracranial hypertension in children: The Iowa experience. J Chold Neurol 9: 144-149.

Baineni, R., Gulati, R., Delhi, C, G, K. (2016) Vitamin a toxicity presenting as bone pain. Arch Dis Child. Epub ahead of print.

Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, Swan G (2014). National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012): https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf

Bates B, Cox L, Nicholson S, Page P, Prentice A, Steer T, Swan G (2016). National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014): https://www.gov.uk/government/statistics/ndns-results-from-years-5-and-6-combined

Bauerfeind J, C. (1980) The safe use of vitamin A. A report of the International Vitamin A Conservative Group (IVACG). The Nutrition Foundation, Washington D.C 1-44.

Biesalski H, K (1989) Comparative assessment of the toxicology of vitamin A and retinoids in man. Toxicology 57:117-161.

Carpenter T, O., Pettifor J,M., Russell R, M., Pitha J., Mobarhan S., Ossip M,S., Wainer s., Anast C,S. (1987) Severe hypervitaminosis Ain siblings: evidence of variable tolerance to retinol intake. J Pediatr111:507-12.

COT (2013) Statement on the potential risks rom high levels of vitamin A in the infant diet. Available at https://cot.food.gov.uk/sites/default/files/cot/cotstavita.pdf

Commission Delegated Regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding (Text with EEA relevance) http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2016.025.01.0001.01.ENG

Department of Health (DH) (1994). The COMA report on Weaning and the Weaning Diet. Report on Health and Social Subjects 45. The Stationary Office London.

Department of Health (DH) (2016). Birth to five. Available at http://www.publichealth.hscni.net/publications/birth-five

Department of Health (DH) (2013). Diet and nutrition survey of infants and young children, 2011.
Available at: http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

EFSA (2015) Scientific opinion: Scientific opinion on dietary reference values for vitamin A. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). EFSA Journal 13 (3): 4028. Available at http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4028/epdf

European Commission. (2006). Commission Directive 2006/141/ec of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC. URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ%3AL%3A2006%3A401%3A0001%3A0033%3AEN%3APDF

FAO/WHO. (2015). Safety evaluation of certain food additives and contaminants: Prepared by the seventy-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series, No. 70, 2015
http://apps.who.int/iris/bitstream/10665/171781/3/9789240693982_eng.pdf

Gamble J, G., Stanley I. (1985) Hypervitaminosis A in a child from megadosing. J Pediatr Ortho 5 (2): 219.

Geubel, A.P., De Galocsy, C., Alves, N., Rahier, J., Dive, C. (1991) Liver damage caused by therapeutic vitamin A administration: Estimate of dose-related toxicity on 41 cases. Gastroenterology 100 (6):1701-1709.

Institute of Medicine (US) Panel on Micronutrients (2001). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academies Press.

Lippe B., Hensen L., Mendoza G., Finerman M., Welch M. (1981) Chronic vitamin A intoxication. A multisystem disease that could reach epidemic proportions. Am J Dis Child 135: 634-636.

Loughrill, E., Govinden, P., Zand, N. (2016) Vitamins A and E content of commercial infant foods in the UK: A cause for concern? Food Chemistry 210: 56-62.

McCance and Widdowson's 'composition of foods integrated dataset' on the nutrient content of the UK food supply (2015).
https://www.gov.uk/government/publications/composition-of-foods-integrated-dataset-cofid

Mendoza F, S., Johnson F., Kerner J,A., Tune B, M., Shocat S,J. (1988) Vitamin A intoxication presenting with ascites and a normal vitamin A level. West J Med 148: 88-90.

Miller J, H., Hayon I, I. (1985) Bone scintigraphy in hypervitaminosis A. AJR 144: 767-768.

NHS (2016) Healthy Start. Available at https://www.healthystart.nhs.uk/for-health-professionals/vitamins/ accessed November 2016.

Patel, P., Hanning, R,M., Atkinson, S, A., Dent, P.B., Dolovich, J. (1988) Intoxication from vitamin A in an asthmatic child. CMAJ 139: 755-756.

Ruby, L.K., Mital, M.A. (1974) Skeletal deformities following chronic hypervitaminosis A. J Bone Joint Surg Am

SCF (2002) Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Preformed Vitamin A (retinol and retinyl esters). SCF/CS/NUT/UPPLEV/24 Final. P1-26. URL: http://ec.europa.eu/food/fs/sc/scf/out145_en.pdf

Search Strategy

General vitamin A exposure search

Websites interrogated –
- EFSA
- COT
- FSA
- JECFA

Scientific publications literature search. Databases interrogated –
- PubMed
- Web of Science

Exclusions: Papers not in the English language. Studies not performed in the UK unless no data available, where EU data was permissible.

Specific search terms:

Milk AND Vitamin A
Search Dates (From/To) – 01/01/11 to 01/09/16

PubMed 213
Web of Science 332

Infant formula* Vitamin A
Search Dates (From/To) – 01/01/11 to 01/09/16

PubMed 26
Web of Science 299

Baby food Vitamin A
Search Dates (From/To) – 01/01/11 to 01/09/16

PubMed 179
Web of Science 75

Hypervitaminosis Vitamin A
Search Dates (From/To) – 01/01/11 to 01/09/16

PubMed 56
Web of Science 160
Medline

Vitamin A and children's diet

Search Dates (From/To) – 01/01/11 to 01/09/16
Exclusion Criteria –
•
•
PubMed 55
Web of Science 132
Medline

Retinol AND exposure
Search Dates (From/To) – 01/01/11 to 01/09/16

PubMed 538
WOS 202

Vitamin A and Weaning
Search Dates (From/To) – 01/01/11 to 01/09/16
PubMed 28
WOS 334

Vitamin A exceed
Search Dates (From/To) – 01/01/11 to 01/09/16
PubMed 16